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Association of Vitamin D Levels with Chronic Liver Disease: A Case-Control Study

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ABSTRACT

Background: Vitamin D plays a critical role in bone metabolism, immune regulation, and cellular function. In patients with chronic liver disease (CLD), hepatic dysfunction impairs vitamin D metabolism, leading to deficiency. Emerging evidence suggests an association between low serum vitamin D levels and worsening liver disease severity. However, there remains a paucity of data exploring this relationship across diverse etiologies of CLD and validated severity indices. Therefore, this study aimed to assess the prevalence of vitamin D deficiency in CLD patients, examine its correlation with different etiologies of liver disease, and evaluate its association with disease severity using Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores.

Methods: A case-control study was conducted at RL Jalappa Hospital, Kolar, over one month. A total of 48 participants were enrolled 24 CLD patients (cases) and 24 healthy individuals (controls), matched for age and sex. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured using ELISA. CLD severity was assessed using CTP and MELD scores. Patients were classified based on vitamin D status into deficient (<20 ng/mL), insufficient (20–29.9 ng/mL), sufficient (30–100 ng/mL), or toxic (>100 ng/mL). Statistical analysis included t-tests, ANOVA, chi-square, and linear regression using SPSS v22, with $p < 0.05$ considered significant.

Results: Vitamin D deficiency was observed in 37.5% of CLD cases versus 16.7% of controls. In CLD patients, vitamin D levels declined with increasing bilirubin and decreasing albumin levels. Patients with bilirubin >3 mg/dL had mean vitamin D levels of 19.76 ± 7.11 ng/mL compared to 25.54 ± 6.78 ng/mL in those with bilirubin <2 mg/dL. Similarly, patients with albumin <3.0 g/dL had lower vitamin D levels (16.68 ± 6.49 ng/mL). Vitamin D levels were inversely associated with MELD and CTP scores. Regression analysis showed significant negative correlations: $r = –0.6554$ (MELD) and $r = –0.7221$ (CTP), $p < 0.0001$.

Conclusion: Vitamin D deficiency is significantly more prevalent in CLD patients than in healthy controls and correlates strongly with disease severity. Routine assessment of serum vitamin D levels in CLD patients may aid in early identification of those at risk of progression and may serve as a valuable prognostic biomarker.

Keywords: *Vitamin D, Chronic liver disease, Cirrhosis, MELD score, Child-Pugh score, Hypovitaminosis D, Liver function, Biomarker, Case-control study, Hepatic dysfunction*

1. INTRODUCTION

Chronic liver disease (CLD) represents a global public health burden, characterized by progressive destruction and regeneration of liver tissue, culminating in fibrosis, cirrhosis, and hepatic failure. The global prevalence of CLD continues to rise, with an increasing incidence of etiologies such as nonalcoholic fatty liver disease (NAFLD), hepatitis B and C infections, and alcohol-related liver injury [1]. As liver function declines, patients often experience multisystemic complications that impact metabolism, immunity, and nutrient absorption.

Vitamin D, a fat-soluble secosteroid hormone, plays a crucial role in calcium and phosphorus metabolism, immune regulation, and cellular proliferation. Beyond its classical role in bone health, emerging research underscores its involvement in various chronic illnesses, including cardiovascular disease, diabetes, autoimmune disorders, and liver disease [2,3]. Vitamin D exists in two primary forms: vitamin D2 (ergocalciferol) derived from plant sources and vitamin D3 (cholecalciferol) synthesized in the skin upon exposure to ultraviolet B rays or ingested through animal-based foods. Once in the body, vitamin D undergoes two hydroxylation steps first in the liver to form 25-hydroxyvitamin D [25(OH)D], and then in the kidneys to produce the biologically active form, 1,25-dihydroxyvitamin D [1,25(OH)2D] [4].

The liver plays a pivotal role in this conversion, and hence, hepatic dysfunction—as seen in CLD can impair vitamin D metabolism. Several studies have shown that vitamin D deficiency is common among patients with liver disease, with prevalence ranging between 64% and 93% depending on geographic region, disease severity, and population studied [5]. Hypovitaminosis D in CLD has been associated with poor clinical outcomes, including hepatic encephalopathy, higher risk of infections, osteoporosis, insulin resistance, and increased mortality [6]. It is now well recognized that vitamin D possesses anti-inflammatory, antifibrotic, and immunomodulatory effects, which may be relevant in the progression and complications of liver disease [7].

Recent research has also linked low serum 25(OH)D levels with increased hepatic fibrosis, portal hypertension, and hepatic decompensation. For example, patients with advanced fibrosis or cirrhosis often demonstrate significantly lower vitamin D concentrations compared to those with early-stage disease [8]. Vitamin D deficiency may further contribute to sarcopenia a critical prognostic factor in cirrhosis due to its role in muscle health and metabolism [9].

Despite the clinical importance of vitamin D in liver physiology and pathology, it remains an underexplored area in routine hepatology practice. Moreover, few studies have evaluated the relationship between vitamin D levels and specific liver disease etiologies (such as hepatitis B, hepatitis C, or NAFLD) and their corresponding impact on severity indices like Child-Turcotte-Pugh (CTP) or MELD scores [10].

The present study aims to address this gap by evaluating serum vitamin D levels in patients with chronic liver disease and comparing them with healthy controls. Additionally, it examines the correlation between vitamin D status and disease severity using validated scoring systems, as well as the etiological patterns of CLD. This investigation may help clarify the potential role of vitamin D as a biomarker and therapeutic adjunct in the management of chronic liver disease.

Objectives

1. To assess the prevalence of vitamin D deficiency among patients with chronic liver disease (CLD).
2. To evaluate the correlation between different etiologies of CLD and serum vitamin D levels.
3. To analyze the association between the severity of CLD and serum vitamin D deficiency using CTP and MELD scores.

2. METHODS

Study Design and Setting

This was a prospective case-control study conducted in the Department of General Medicine at Sri Devaraj Urs Medical College, RL Jalappa Hospital, Kolar. The study was carried out over a period of one month, from December 2024 to January 2025.

Study Population

A total of 48 participants were enrolled in the study, including 24 cases (patients diagnosed with chronic liver disease) and 24 age- and sex-matched healthy individuals who served as controls. All participants were recruited from the inpatient department after obtaining written informed consent.

Inclusion and Exclusion Criteria

Patients aged 18 years and above with a confirmed diagnosis of chronic liver disease (CLD), as per clinical, biochemical, and radiological criteria, were included. The severity of CLD was assessed using the Child-Turcotte-Pugh (CTP) score and the Model for End-Stage Liver Disease (MELD) score. Exclusion criteria included patients with chronic kidney disease, malignancy, those on steroid therapy for rheumatological conditions, those receiving vitamin D supplementation, and those who refused consent.

Clinical and Laboratory Evaluation

All participants underwent comprehensive clinical evaluation, including history taking and physical examination. Investigations performed included complete blood count, liver function tests, renal function tests, coagulation profile, hepatitis B surface antigen (HBsAg), anti-HCV antibodies, abdominal ultrasonography, and upper gastrointestinal endoscopy for cases.

Vitamin D Estimation

Approximately 2 mL of venous blood was drawn from each participant in a light-protected vial. The serum was separated by centrifugation and stored at –20°C until analysis. Serum 25-hydroxyvitamin D [25(OH)D] levels were estimated using a commercial enzyme-linked immunosorbent assay (ELISA) kit. The method involved competitive immunoassay with fluorescent detection. Fluorescence intensity, measured at 450 nm, was inversely proportional to serum vitamin D concentration. Final values were automatically calculated using calibration curves stored in the analyzer software and expressed in ng/mL.

Classification of Vitamin D Status

Participants were categorized based on serum vitamin D levels into four groups:

1. Deficiency: <20 ng/mL
2. Insufficiency: 20–29.9 ng/mL
3. Sufficiency: 30–100 ng/mL
4. Potential toxicity: >100 ng/mL

For CLD patients, the following were also recorded: etiology of liver disease (e.g., hepatitis B, hepatitis C, nonalcoholic steatohepatitis [NASH], autoimmune hepatitis, alcohol-related liver disease), CTP score, and MELD score.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between groups were made using the unpaired t-test for two groups and ANOVA for more than two groups. Categorical variables were presented as frequencies and percentages, and analyzed using the chi-square test. Linear regression analysis was used to determine the correlation between serum vitamin D levels and severity of CLD as assessed by CTP and MELD scores. A p-value of <0.05 was considered statistically significant.

3. RESULTS

Comparison of Vitamin D Levels Between Cases and Controls

Vitamin D Level (ng/mL)	CLD Cases (n = 24)	Controls (n = 24)
<10	3 (12.5%)	1 (4.2%)
10–20	6 (25%)	3 (12.5%)
21–30	10 (41.7%)	7 (29.2%)
>30	5 (20.8%)	13 (54.2%)

Among the 24 patients with chronic liver disease (CLD), 37.5% were found to have vitamin D deficiency (<20 ng/mL), and an additional 41.7% had insufficient levels (21–30 ng/mL), indicating that 79.2% of the CLD cases had suboptimal vitamin D levels. In contrast, only 16.7% of the controls had vitamin D deficiency, and 29.2% had insufficient levels, while more than half of the control group (54.2%) had normal vitamin D levels (>30 ng/mL). This reflects a clear disparity in vitamin D status between cases and controls, suggesting that patients with CLD are significantly more likely to have deficient or insufficient vitamin D levels.

Vitamin D Level in Relation to Serum Bilirubin in CLD Cases

Serum Bilirubin (mg/dL)	<2 (n = 8)	2–3 (n = 4)	>3 (n = 12)	P-value	Significance
Vitamin D (ng/mL) Mean ± SD	25.54 ± 6.78	21.87 ± 4.05	19.76 ± 7.11	0.0004	Yes

There was a decreasing trend in mean vitamin D levels with rising serum bilirubin levels. Patients with bilirubin <2 mg/dL had a mean vitamin D level of 25.54 ± 6.78 ng/mL, which progressively declined to 21.87 ± 4.05 ng/mL for those with bilirubin between 2–3 mg/dL, and further to 19.76 ± 7.11 ng/mL in patients with bilirubin >3 mg/dL. The difference was

statistically significant (p = 0.0004), indicating that worsening liver function, as reflected by hyperbilirubinemia, is associated with lower serum vitamin D levels.

Vitamin D Level in Relation to Serum Albumin in CLD Cases

Serum Albumin (g/dL)	>3.5 (n = 6)	3.0–3.5 (n = 10)	<3.0 (n = 8)	P-value	Significance
Vitamin D (ng/mL) Mean ± SD	27.64 ± 7.33	21.73 ± 5.02	16.68 ± 6.49	<0.0001	Yes

Patients with lower serum albumin levels were more likely to have lower vitamin D concentrations. Those with albumin >3.5 g/dL had the highest mean vitamin D level (27.64 ± 7.33 ng/mL), while those with albumin between 3.0–3.5 g/dL had a mean level of 21.73 ± 5.02 ng/mL. The lowest mean vitamin D (16.68 ± 6.49 ng/mL) was observed in patients with serum albumin <3.0 g/dL. This trend was statistically significant (p < 0.0001), supporting the notion that declining synthetic function of the liver is associated with worsening vitamin D deficiency.

Vitamin D Level in Relation to MELD Score in CLD Cases

MELD Score Group	<9 (n = 1)	10–19 (n = 11)	20–24 (n = 8)	30–39 (n = 2)	>40 (n = 2)	P-value	Significance
Vitamin D (ng/mL) Mean ± SD	32.68 ± 2.23	24.96 ± 6.21	19.34 ± 6.47	14.43 ± 4.18	8.42 ± 1.19	<0.0001	Yes

Vitamin D levels decreased significantly with increasing MELD scores, reflecting disease severity. Patients with a MELD score <9 had a mean vitamin D level of 32.68 ± 2.23 ng/mL, while those with scores of 10–19, 20–24, 30–39, and >40 had progressively lower levels of 24.96 ± 6.21, 19.34 ± 6.47, 14.43 ± 4.18, and 8.42 ± 1.19 ng/mL, respectively. The association was statistically significant (p < 0.0001), indicating a strong inverse relationship between vitamin D levels and MELD score.

Vitamin D Level in Relation to Child-Pugh Score in CLD Cases

CTP Class	A (5–6) (n = 3)	B (7–9) (n = 12)	C (10–15) (n = 9)	P-value	Significance
Vitamin D (ng/mL) Mean ± SD	32.41 ± 3.83	22.58 ± 5.32	15.31 ± 5.92	<0.0001	Yes

A consistent decline in serum vitamin D levels was also observed across worsening Child-Pugh (CTP) classes. Patients in Class A had a mean vitamin D level of 32.41 ± 3.83 ng/mL, which dropped to 22.58 ± 5.32 ng/mL in Class B and 15.31 ± 5.92 ng/mL in Class C. The trend was statistically significant (p < 0.0001), reinforcing that lower vitamin D levels are associated with more advanced liver dysfunction as classified by the Child-Pugh scoring system.

Correlation of Vitamin D Level with Severity Scores in CLD Cases

Parameter	r Value	P-value	Significance
Child-Pugh Score	–0.7221	<0.0001	Yes
MELD Score	–0.6554	<0.0001	Yes

Linear regression analysis demonstrated a significant negative correlation between vitamin D levels and both CTP and MELD scores. The correlation coefficient for CTP score was –0.7221, and for MELD score, it was –0.6554, with both associations showing high statistical significance (p < 0.0001). This implies that as the severity of liver disease increases,

serum vitamin D levels decrease proportionally, making vitamin D a potential marker of liver disease progression.

4. DISCUSSION

This case-control study assessed the association between serum vitamin D levels and chronic liver disease (CLD), focusing on disease severity and relevant biochemical parameters. Our results indicate that vitamin D deficiency is significantly more prevalent among CLD patients than in healthy controls and that serum vitamin D levels are inversely correlated with disease severity as measured by both the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores.

In our study, 37.5% of CLD patients had vitamin D deficiency (<20 ng/mL), and 41.7% had insufficiency (21–30 ng/mL), indicating that nearly 80% of the CLD population had suboptimal vitamin D levels. This is in agreement with the findings by Khan et al., who reported 81.4% subnormal vitamin D levels in cirrhotic patients [8]. In comparison, more than half (54.2%) of our control group had sufficient vitamin D levels, reinforcing the association between hepatic dysfunction and hypovitaminosis D. Similar trends were observed by Fisher et al., who documented inadequate 25(OH)D levels in over 90% of patients with cirrhosis [9].

Vitamin D deficiency in CLD arises from several mechanisms including impaired hepatic hydroxylation, reduced vitamin D binding protein (DBP) production, and decreased bioavailability due to low albumin levels. In our study, patients with serum albumin <3.0 g/dL had the lowest mean vitamin D levels (16.68 ± 6.49 ng/mL), which aligns with the findings of Bikle et al., who showed that hypoalbuminemia and DBP deficiency directly reduce circulating vitamin D levels in liver disease [10].

We also noted a significant inverse relationship between vitamin D levels and serum bilirubin. Patients with bilirubin >3 mg/dL had a mean vitamin D of 19.76 ± 7.11 ng/mL, consistent with the observations of Okubo et al., who demonstrated a similar trend in CLD patients with cholestasis [11]. Reduced bile salt-dependent absorption and altered vitamin D metabolism are likely contributors.

A striking feature of our results was the progressive decline in serum vitamin D levels with increasing MELD and CTP scores. For example, mean vitamin D dropped from 32.68 ng/mL in patients with MELD <9 to just 8.42 ng/mL in those with MELD >40. Likewise, levels declined from 32.41 ng/mL in CTP Class A to 15.31 ng/mL in Class C. These findings are supported by Miroliaee et al., who demonstrated a significant negative correlation between vitamin D and both MELD ($r = –0.507$) and CTP ($r = –0.524$) scores [12]. Similarly, Finkelmeier et al. reported that severely deficient 25(OH)D3 levels were prevalent in patients with high MELD scores and were linked with worse outcomes [13].

Our linear regression analysis showed correlation coefficients of –0.7221 and –0.6554 with CTP and MELD scores respectively, both with high statistical significance ($p < 0.0001$). These values support the work of Putz-Bankuti et al., who proposed that serum vitamin D can serve as a reliable surrogate marker of hepatic decompensation [14].

In addition to severity prediction, vitamin D is known to possess anti-inflammatory and antimicrobial properties, which may influence outcomes in CLD. Although our study did not find a statistically significant link between vitamin D deficiency and infection risk, patients with leukocytosis tended to have lower vitamin D levels. Anty et al. reported a significant association between severe vitamin D deficiency and increased risk of bacterial infections in cirrhotic patients [15]. Moreover, Finkelmeier et al. observed that cirrhotic patients with ongoing infections had significantly lower serum vitamin D levels compared to those without infection [13].

Genetic and environmental factors also affect vitamin D metabolism. Wang et al. identified polymorphisms in genes like **GC**, **DHCR7**, and **CYP2R1**, which alter serum vitamin D levels and may influence disease susceptibility and severity in liver disease [16]. These insights support the consideration of genetic screening and personalized supplementation strategies in CLD management.

Finally, growing evidence suggests that vitamin D supplementation may offer therapeutic benefits. A recent Cochrane review by Bjelakovic et al. concluded that vitamin D supplementation may improve immune and liver function parameters in CLD, although more robust trials are needed [17].

Taken together, our findings support routine screening for vitamin D deficiency in CLD patients and highlight its strong association with liver dysfunction severity. Further longitudinal and interventional studies are needed to explore the potential therapeutic role of correcting hypovitaminosis D in this population.

5. CONCLUSION

This study highlights a significant association between vitamin D deficiency and chronic liver disease (CLD), with nearly 80% of CLD patients exhibiting suboptimal serum vitamin D levels. The inverse correlation observed between vitamin D levels and both MELD and Child-Turcotte-Pugh (CTP) scores suggests that declining vitamin D may reflect worsening hepatic function. Additionally, reduced vitamin D levels were found in patients with higher bilirubin and lower albumin, indicating its close link with liver synthetic and excretory dysfunction. Compared to healthy controls, CLD patients had markedly poorer vitamin D status, reinforcing the impact of liver disease on vitamin D metabolism. These findings underscore the importance of routine screening for vitamin D deficiency in CLD patients. Early detection and correction of

hypovitaminosis D may serve as a supportive strategy to improve nutritional status, modulate immune function, and potentially delay disease progression. Further longitudinal and interventional studies are warranted to validate these findings.

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